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EDITORIAL COMMENT

Pre-Procedural Blood Glucose Levels

A New Risk Marker for Contrast-Induced Acute Kidney Injury in Patients Without Diabetes With Acute Myocardial Infarction*

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Contrast-induced acute kidney injury (AKI) is a common complication of procedures requiring the use of iodinated radiographic contrast media (1–5). It is the third most common cause of acute renal failure in hospitalized patients and is associated with higher short- and long-term morbidity and mortality rates than are observed in patients without contrast-induced AKI (1–13).

The term "contrast-induced AKI" is favored by many experts over the more familiar "contrast-induced nephropathy" (CIN) because it acknowledges that deterioration of renal function after procedures that require the use of iodinated contrast media may be multifactorial (1). CIN is in fact a form of contrast-induced AKI but is not the only mechanism for its occurrence (1–5).

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Broadly speaking, contrast-induced AKI is defined as an increase in the serum creatinine level beginning within the first 24 h after contrast exposure and peaking in most patients up to 5 days after exposure (1–5). Most definitions have required a 0.5 to 1.0 mg/dl increase in the serum creatinine level and/or a rise in the serum creatinine level to 25% to 50% above baseline (1–5). The most commonly used definition is an increase in the serum creatinine level ≥0.5 mg/dl or a rise in the serum creatinine level of 25% or more from baseline when assessed 48 hours after contrast exposure (1–5). Most recently, the Acute Kidney Injury Network has defined contrast-induced AKI as a rise in the serum creatinine level ≥0.3 mg/dl or an increase in the serum creatinine level of 50% or more from baseline (1).

The incidence of contrast-induced AKI depends in part on the definition used and on a variety of patient-related and procedure-related factors (1–5,14). In a survey of representative studies assessing the clinical and renal consequences of iodinated contrast media use from 1976 to 2005, Finn (3) reported an incidence of CIN that ranged from 3.3% to 31.0%. McCullough (1) estimated that the overall incidence of contrast-induced AKI has decreased from approximately 15% to 7% over the past decade, because of greater awareness of risk markers for the development of this syndrome, the development of less toxic contrast agents, and possibly the use of therapeutic interventions to reduce risk. The incidence of contrast-induced AKI rises progressively with the number of risk markers and is particularly high in patients with pre-existing chronic kidney disease and diabetes mellitus (1–5,14). In patients without risk markers, the reported incidence of contrast-induced AKI has been <2% in most studies (1–6,14). The incidence remains low in patients with normal renal function (even if they have diabetes). The incidence increases to 4% to 11% in patients with mild to moderate renal insufficiency but rises to 40% or more in patients with volume depletion or advanced heart failure (1–5). The reported incidence of contrast-induced AKI ranges from 9% to 30% in patients with mild to moderate renal insufficiency and diabetes mellitus and rises to 50% to 90% in those with severe renal insufficiency and diabetic nephropathy (1–5).

Contrast-induced AKI has been associated with an increased mortality risk, particularly in patients undergoing percutaneous coronary intervention (PCI) (1–13). Studies of patients undergoing PCI, including those with acute myocardial infarction, have reported in-hospital mortality rates ranging from 6.3% to 31.0% in patients with and from 0.6% to 4.9% in those without contrast-induced AKI or CIN (1–11). In-hospital mortality rates in PCI patients requiring dialysis range from 22.6% to 35.7% (1–5,8,9). Mortality rates at 1 year range from 12.1% to 37.7% in patients with and from 3.7% to 14.4% in those without contrast-induced AKI or CIN (1–11).

Risk markers for contrast-induced AKI may be classified as patient- or procedure-related (1–5,15–18). The most important patient-related risk factor is pre-existing impairment of renal function. Patients whose estimated glomerular filtration rates are <60 ml/min/1.73 m^2 are thought to have impaired renal vasodilation and reduced clearance of contrast media, thus facilitating the hemodynamic changes and tubular toxicity associated with use of these agents (1–5,15–19). Diabetes mellitus has been cited as a risk marker for contrast-induced AKI. This is clearly true when diabetes mellitus is associated with chronic kidney disease, particularly diabetic nephropathy (1–5,15–17). Opinion is divided as to whether diabetes mellitus alone serves as a risk marker for contrast-mediated AKI (1–5). Older age also appears to be a risk factor for contrast-induced AKI (1–15,17). Advanced congestive heart failure and a moder-

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ate to severely reduced left ventricular ejection fraction have been shown to be independent predictors of contrast-induced AKI, possibly related to impaired renal vasodilation (1–6,16). Hypovolemia and states characterized by low effective intravascular volume (cirrhosis, anemia) have also been identified as risk markers of contrast-induced AKI due in part to abnormal renal vasodilatory responses and decreased clearance of contrast media (1–5,15). Similarly, hypotension regardless of cause also serves as a risk marker (1–5,15). Nephrotoxic drugs increase the sensitivity of the kidney to iodinated contrast media (1–5,15). These include nonsteroidal anti-inflammatory drugs, sulfonamide, and aminoglycoside agents alone or in combination with loop diuretic agents (1–5,15). Cyclosporine A, mannitol, and amphotericin B also contribute to contrast-induced renal injury by various mechanisms (1–5,15). Metformin, although not nephrotoxic, facilitates contrast-induced AKI (1–5). Multiple myeloma is also considered a risk marker. Both male and female sex, hypertension, acute myocardial infarction, multivessel coronary artery disease, peripheral artery disease, renal artery stenosis, hyperuricemia, and the metabolic syndrome have been suggested as possible patient-related risk markers on the basis of individual studies, but further research is required to confirm these findings (1–5,15,18).

Procedure-related risk markers for contrast-induced AKI include the use of high-osmolar ionic contrast media, low-osmolar contrast media (compared with nonionic isoosmolar contrast media), high volumes of contrast media, and multiple procedures requiring contrast media within 72 h (1–5,10,15–18). PCI or peripheral artery intervention, coronary artery bypass surgery, and use of an intra-aortic balloon pump (all of which predispose to atheroemboli) represent additional procedure-related risk markers for contrast-induced AKI (1–5,15). Mehran et al. (16) developed and validated a risk score for the prediction of CIN after PCI using many of the aforementioned risk markers.

The pathophysiology of contrast-induced AKI is not well understood. Atheroemboli and hemodynamic alterations leading to reduced renal perfusion may play a role in some cases, as may other comorbidities that predispose patients receiving iodinated contrast to renal injury (1–5). Impaired renal function at baseline (estimated glomerular filtration rate <60 ml/min/1.73 m^2) appears to be a prerequisite to contrast-induced AKI (1–5). Two major theories exist to explain this phenomenon: renal vasoconstriction and tubular injury (1–5). Renal vasoconstriction is mediated by adenosine, endothelin, the high osmolarity of some contrast agents, and blockade of endogenous vasodilators such as nitric oxide and local prostaglandins (1–5). Renal blood flow decreases up to 30% 2 h after contrast exposure and up to 50% 4 h after exposure (1–5). This, in association with volume depletion or reduced renal blood flow from heart failure, leads to increased viscosity, which predisposes to medullary hypoxia and ischemia (1–5). This process may be facilitated by interstitial edema and may lead to loss of renal tubular cells (1–5). Tubular injury is thought to result from a direct cytotoxic effect of iodinated contrast media, probably mediated by oxidative stress and the generation of reactive oxygen species (1–5). Stasis of contrast media in renal tubules may contribute to this phenomenon (1–5).

The study by Stolker et al. (19) in this issue of the *Journal* demonstrates that pre-procedural blood glucose levels are a risk marker for contrast-induced AKI in patients without diabetes with acute myocardial infarction who undergo coronary angiography during their index admissions. Such was not observed in patients with diabetes, perhaps because of higher baseline risk for contrast-induced AKI in that population. These observations remained valid even after adjusting for confounding variables, most importantly impaired renal function at baseline. In a previous study, fasting blood glucose was found to be an independent predictor of contrast-induced AKI within the context of the metabolic syndrome (18). The study by Stolker et al. (19) is the first to document an increase in the risk for contrast-induced AKI with progressive elevations of blood glucose levels. Hyperglycemia in patients without diabetes is commonly observed in critically ill patients and occurs in more than 40% of patients without diabetes with acute myocardial infarction (20). The etiology of hyperglycemia in this setting is uncertain but may relate in part to stress-related neurohormonal alterations, including stimulation of catecholamines, activation of the renin-angiotensin-aldosterone system, and expression of various cytokines (20). In the critical care population, hyperglycemia in patients without diabetes is seen by some as a "stress test" denoting the failure of endogenous insulin reserves to adequately control blood glucose (20). Others have postulated that hyperglycemia occurs because of insulin resistance (20). Whether these mechanisms account for hyperglycemia in patients with acute myocardial infarction is uncertain. The results of this study are important not only because they identify a new risk marker for contrast-induced AKI in patients without diabetes with acute myocardial infarction but because they raise the question of whether interventions such as intensive insulin therapy might reduce risk in this population. It is tempting, but premature, to extend the findings in this study to patients without diabetes undergoing elective coronary angiography and PCI. Further studies are necessary to determine if pre-procedural hyperglycemia serves as a risk marker for contrast-induced AKI in populations other than those with acute myocardial infarction who receive iodinated contrast media during coronary angiography.

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